

WHAT IS CLAIMED IS:

1. An isolated or purified human nucleic acid molecule encoding a human protein that is expressed ubiquitously in human cells, wherein said protein has the potential of generating a plurality of protein fragments binding with high affinity to a human HLA molecule.

2. The nucleic acid of claim 1, wherein said human protein is overexpressed in proliferative cells.

3. The nucleic acid of claim 2, wherein said proliferative cells are tumoral cells and wherein expression of said protein is essential for the tumoral cell's survival.

4. The nucleic acid of claim 1, wherein said human protein is a functional or structural homolog of yeast STT3 (SEQ ID NO: 6).

5. The nucleic acid of claim 1, wherein said human protein is a paralog of human ITM1 (SEQ ID NO: 12).

6. The nucleic acid of claim 1, comprising a polynucleotide having a nucleotide sequence coding an amino acid sequence selected from the group consisting of:

a) an amino acid sequence having greater than 71% amino acid sequence identity to SEQ ID NO:8;

b) an amino acid sequence having greater than 71% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO:7;

c) an amino acid sequence having greater than 82% amino acid sequence homology to SEQ ID NO: 8;

d) an amino acid sequence having greater than 82% amino acid sequence homology to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 7;

- e) an amino acid sequence having greater than 97% amino acid sequence identity to SEQ ID NO: 2;
- f) an amino acid sequence having greater than 97% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1;
- 5 g) an amino acid sequence having greater than 97% amino acid sequence homology to SEQ ID NO: 2; and
- h) an amino acid sequence having greater than 97% amino acid sequence homology to an amino acid sequence encoded by an open reading frame
- 10 having SEQ ID NO: 1.

7. The nucleic acid of claim 6, comprising a polynucleotide having a nucleotide sequence coding an amino acid sequence selected from the group consisting of:

- a) an amino acid sequence 100% identical to SEQ ID NO: 2 ; and
- 15 b) an amino acid sequence 100% identical to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1.

8. The nucleic acid of claim 1, comprising a polynucleotide having a nucleotide sequence selected from the group consisting of:

- 20 a) a nucleotide sequence having greater than 63% nucleotide sequence identity with SEQ ID NO:7;
- b) a nucleotide sequence having greater than 63% nucleotide sequence identity with a nucleic acid encoding an amino acid sequence of SEQ ID NO:8
- c) a nucleotide sequence having at least 91% nucleotide sequence identity with
- 25 SEQ ID NO: 1; and
- d) a nucleotide sequence having at least 91% nucleotide sequence identity with a nucleic acid encoding an amino acid sequence of SEQ ID NO: 2.

9. The nucleic acid of claim 8, comprising a polynucleotide 100% identical to

30 identical to SEQ ID NO: 1.

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10. The nucleic acid of claim 1, wherein said HLA molecule is selected from the group consisting of HLA molecules listed in Table 1.

11. An isolated or purified human nucleic acid molecule comprising a polynucleotide having a nucleotide sequence selected from the group consisting of:

- a) a nucleotide sequence having greater than 63% nucleotide sequence identity with SEQ ID NO: 7;
- b) a nucleotide sequence having greater than 63% nucleotide sequence identity with a nucleic acid encoding an amino acid sequence of SEQ ID NO:8;
- c) a nucleotide sequence having at least 91% nucleotide sequence identity with SEQ ID NO: 1;
- d) a nucleotide sequence having at least 91% nucleotide sequence identity with a nucleic acid encoding an amino acid sequence of SEQ ID NO: 2; and
- e) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c) or (d).

12. The nucleic acid molecule of claim 11, wherein it comprises a polynucleotide having a nucleotide sequence selected from the group consisting of:

- a) a nucleotide sequence having at least 91% nucleotide sequence identity with SEQ ID NO: 1;
- b) a nucleotide sequence having at least 91% nucleotide sequence identity with a nucleic acid encoding an amino acid sequence of SEQ ID NO: 2; and
- c) a nucleotide sequence complementary to any of the nucleotide sequences in (a), or (b).

13. The nucleic acid of claim 12, comprising a polynucleotide selected from the group consisting of:

- a) a polynucleotide having a nucleotide sequence 100% identical to SEQ ID NO: 1;

- b) a polynucleotide having a nucleotide sequence complementary to SEQ ID NO: 1;
- c) a polynucleotide having at least 15 nucleotides of the polynucleotide of (a) or (b).

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14. An isolated or purified nucleic acid molecule which hybridizes under high stringency conditions to any of the nucleic acid molecules of claim 13.

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15. An isolated or purified human nucleic acid molecule comprising a polynucleotide having the SEQ ID NO: 1, or degenerate variants thereof, and encoding a human SIMP polypeptide.

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16. The nucleic acid of claim 15, encoding the amino acid sequence of SEQ ID NO: 2 or a fragment thereof.

17. The nucleic acid of claim 15, wherein said nucleic acid is cDNA.

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18. An isolated or purified human protein that is expressed ubiquitously in human cells, wherein said protein has the potential of generating a plurality of protein fragments binding with high affinity to a human HLA molecule.

19. The protein of claim 18, wherein said human protein is overexpressed in proliferative cells.

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20. The protein of claim 19, wherein said proliferative cells are tumoral cells and wherein expression of said protein is essential for the tumoral cell's survival.

21. The protein of claim 18, wherein said human protein is a functional or a structural homolog of yeast STT3 (SEQ ID NO:8).

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22. The protein of claim 18, wherein said human protein is a paralog of human ITM1 (SEQ ID NO: 12).

23. The protein of claim 18, wherein said fragments are selected from those comprising at least eight sequential amino acids of SEQ ID NO: 2.

5 24. The protein of claim 18, wherein said fragments are selected from the group consisting of the peptides listed in Table 1.

25. The protein of claim 18, wherein said HLA molecule is selected from the group consisting of HLA molecules listed in Table 1.

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26. The protein of claim 18, wherein it comprises an amino acid sequence selected from the group consisting of:

- a) an amino acid sequence having greater than 71% amino acid sequence identity to SEQ ID NO: 8;
- 15 b) an amino acid sequence having greater than 71% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 7;
- c) an amino acid sequence having greater than 82% amino acid sequence homology to SEQ ID NO: 8;
- 20 d) an amino acid sequence having greater than 82% amino acid sequence homology to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 7;
- e) an amino acid sequence having greater than 97% amino acid sequence identity to SEQ ID NO: 2;
- 25 f) an amino acid sequence having greater than 97% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1;
- g) an amino acid sequence having greater than 97% amino acid sequence homology to SEQ ID NO: 2; and
- 30 h) an amino acid sequence having greater than 97% amino acid sequence homology to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1.

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27. The protein of claim 18, wherein it comprises an amino acid sequence selected from the group consisting of:

- a) an amino acid sequence 100% identical to SEQ ID NO: 2; and
- 5 b) an amino acid sequence 100% identical to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1.

28. An isolated or purified polypeptide comprising an amino acid sequence selected from the group consisting of:

- 10 a) an amino acid sequence having greater than 71% amino acid sequence identity to SEQ ID NO: 8;
- b) an amino acid sequence having greater than 71% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 7;
- 15 c) an amino acid sequence having greater than 82% amino acid sequence homology to SEQ ID NO: 8;
- d) an amino acid sequence having greater than 82% amino acid sequence homology to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 7;
- 20 e) an amino acid sequence having greater than 97% amino acid sequence identity to SEQ ID NO: 2;
- f) an amino acid sequence having greater than 97% amino acid sequence identity to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1;
- 25 g) an amino acid sequence having greater than 97% amino acid sequence homology to SEQ ID NO: 2; and
- h) an amino acid sequence having greater than 97% amino acid sequence homology to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1

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29. The polypeptide of claim 28, wherein it comprises an amino acid sequence selected from the group consisting of:

- a) an amino acid sequence 100% identical to SEQ ID NO: 2;
b) an amino acid sequence 100% identical to an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1; and
c) an amino acid sequence consisting of at least eight consecutive amino acids of (a) or (b).

30. The polypeptide of claim 29, wherein it has the potential of generating a plurality of protein fragments binding with high affinity to a human HLA molecule.

31. A substantially pure human SIMP polypeptide, or fragment thereof.

32. The polypeptide or fragment of claim 31, wherein it comprises an amino acid sequence having greater than 97% amino acid sequence homology with a polypeptide selected from the group consisting of:

- a) a polypeptide having SEQ ID NO: 2;
b) a polypeptide having an amino acid sequence encoded by an open reading frame having SEQ ID NO: 1; and
c) a polypeptide that is a fragment of (a) or (b).

33. The polypeptide or fragment of claim 32, wherein said amino acid sequence identity is about 100%.

34. A substantially pure human polypeptide that is encoded by the nucleic acid of claim 1.

35. An isolated or purified human protein that is a paralog of a human protein having SEQ ID NO:12.

36. The human protein of claim 35, wherein it comprises an amino acid sequence having at least 25% identity or at least 25% homology with SEQ ID NO:12.

37. The human protein of claim 36, wherein said percentage of identity and homology are of at least 50% respectively.

38. The protein of claim 37, wherein said percentage of identity and homology are about 56% and 59% respectively.

39. An isolated or purified polypeptide fragment, said fragment comprising at least eight sequential amino acids of SEQ ID NO: 2.

40. An isolated or purified polypeptide having a high binding affinity for a human HLA molecule, said polypeptide comprising at least eight amino acids having a sequence identity that is greater than 97% to a portion of a human protein that is expressed ubiquitously in human cells.

41. The polypeptide of claim 40, wherein said human protein is overexpressed in proliferative cells.

42. The polypeptide of claim 41, wherein said proliferative cells are tumoral cells and wherein expression of said protein is essential for the tumoral cell's survival.

43. The polypeptide of claim 40, wherein said human protein is a functional or structural homolog of yeast STT3 (SEQ ID NO: 6).

44. The nucleic acid of claim 40, wherein said human protein is a paralog of human ITM1 (SEQ ID NO: 12).

45. The polypeptide of claim 40, wherein it comprises at least eight sequential amino acids of SEQ ID NO: 2.

46. The polypeptide of claim 40, wherein it comprises an amino acid sequence encoded by a nucleotide sequence comprising at least 24 sequential nucleic acid of SEQ ID NO: 1.

5 47. The polypeptide of claim 40, wherein it is selected from the group consisting of the peptides listed in Table 1.

48. An antisense nucleic acid which hybridizes under high stringency condition to SEQ ID NO: 1 or to a complementary sequence thereof.

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49. An antisense nucleic acid that reduces human SIMP⁺ cellular levels of expression.

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50. The antisense of claim 49, wherein said antisense hybridizes under high stringency conditions to a genomic sequence or to a mRNA.

51. The antisense of claim 49, wherein said antisense is complementary to a nucleic acid sequence encoding a protein having SEQ ID NO: 2 or a fragment thereof.

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52. A pharmaceutical composition comprising a human SIMP antisense nucleic acid.

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53. A method for eliminating tumoral cells in a mammal, comprising the step of injecting, into said mammal's circulatory system, T-lymphocytes that recognize a immune complex that is present at the surface of said tumoral cells, said immune complex consisting of a SIMP protein fragment or a ITM1 protein fragment bound to an MHC molecule.

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54. The method of claim 53, wherein said mammal is a human.

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55. The method of claim 54, wherein immune complex consists of a hSIMP protein fragment bound to a HLA molecule, and wherein said hSIMP protein fragment comprises at least eight sequential amino acids of SEQ ID NO: 2.

5 56. The method of claim 55, wherein said hSIMP protein fragment is selected from the group consisting of the peptides listed in Table 1.

57. The method of claim 53, wherein said ITM1 protein fragment comprises at least eight sequential amino acids of SEQ ID NO: 12.

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58. A method for increasing cell proliferation in a mammal, comprising the step of: i) contacting said cell with a SIMP polypeptide; and/or ii) increasing cellular expression levels of a SIMP polypeptide.

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59. A method for modulating tumoral cell survival or for eliminating a tumoral cell in a mammal, comprising the step of reducing cellular expression levels of a SIMP polypeptide.

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60. The method of claim 59, wherein said mammal is human, the method comprising the step of the step of delivering a human SIMP antisense into the tumoral cell.

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61. A method for modulating an immune response in a mammal, comprising increasing in lymphoid cells of said mammals the cellular expression levels of a SIMP polypeptide.

62. The method of claim 61, for increasing the level and/or the duration of an antigen-primed lymphocyte proliferation.

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63. The method of claim 61, comprising transfecting lymphocytes with a cDNA coding for a SIMP polypeptide.

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64. The method of claim 61, wherein said mammal is human.

65. A method for decreasing lymphoid cells proliferation, comprising decreasing in said cells cellular expression levels of a SIMP polypeptide.

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66. The method of claim 65, for suppressing an immune response responsible for an autoimmune disease or a transplant rejection.

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67. The method of claim 65, comprising delivering a SIMP antisense into said lymphoid cells.

68. A nucleotide probe comprising a sequence of at least 15 sequential nucleotides of SEQ ID NO: 1 or of a sequence complementary to SEQ ID NO: 1.

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69. A substantially pure nucleic acid that hybridizes to a probe of at least 40 nucleotides in length, said probe derived from SEQ ID NO:1, wherein said nucleic acid hybridizes to said probe under high stringency conditions.

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70. A purified antibody that specifically binds to a purified mammalian SIMP polypeptide.

71. The antibody of claim 70, wherein the mammalian SIMP polypeptide is a human SIMP polypeptide.

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72. The antibody of claim 70, wherein it binds to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

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73. A monoclonal or polyclonal antibody which recognizes the human SIMP polypeptide, or fragment thereof as claimed in claim 31.

74. A method for determining the amount of a SIMP polypeptide in a biological sample, comprising the step of contacting said sample with the antibody of claim 70 or with a probe according to claim 68.

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75. A method of diagnosis of a cancer in a human subject comprising the step of determining the amount of a human SIMP polypeptide in a cell or a biological sample from said subject, wherein said amount is indicative of a probability for said subject of harboring proliferating tumoral cells.

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76. The method of 75, wherein said proliferating tumoral cells grow rapidly and display a short doubling time.

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77. The method of 75, wherein said cancer is selected from the group consisting of: lung cancers, intestine cancers, sarcomas, prostate cancer, testis cancer, breast cancer, melanomas, pancreatic cancer and hematologic cancers.

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78. A kit for determining the amount of a SIMP polypeptide in a sample, said kit comprising the antibody of claim 70 and or a probe according to claim 68, and at least one element selected from the group consisting of instructions for using said kit, reaction buffer(s), and enzyme(s).

79. A transformed or transfected cell that contains the nucleic acid of claim 1.

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80. A transgenic animal generated from the cell of claim 79, wherein said nucleic is expressed in said transgenic animal.

81. A cloning or expression vector comprising the nucleic acid of claim 1.

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82. The vector of claim 81, wherein said vector is capable of directing expression of the peptide encoded by said nucleic acid in a vector-containing cell.

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83. A method for producing a human SIMP polypeptide comprising:
- providing a cell transformed with a nucleic acid sequence encoding a human SIMP polypeptide positioned for expression in said cell;
 - culturing said transformed cell under conditions suitable for expressing said nucleic acid; and
 - producing said hSIMP polypeptide.

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